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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/617,116	07/14/2000	Manish Aghi	0609.4830001/JAG/KRM	5851

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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

S.M.

Advisory Action	Application No.	Applicant(s)	
	09/617,116	AGHI ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 31 October 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☒ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *14-36*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

DAVID GUZO
PRIMARY EXAMINER

Continuation of 2. NOTE: The limitation "attenuated prokarytotic vector" in the proposed claim 28 raises new issues that would require further consideration, particularly 112 first paragraph and second paragraph. For example, how can a prokaryotic vector (e.g., a prokaryotic expression plasmid) be attenuated? Additionally, while the specification discloses the use of a tumor targeted bacterial vector (page 19, lines 28-29), there is no written or literal support for the use of any attenuated prokaryotic vector in the methods of the proposed claims.

Continuation of 5. does NOT place the application in condition for allowance because: Applicants' amendments and arguments have not overcome the rejections of record.

A. With respect to rejections under 35 U.S.C. 112, first paragraph on the issues of using any prokaryotic vector and mammalian artificial chromosome, Applicants presented the same arguments as those in previous Amendments which were not found persuasive for the reasons already set forth in the Final Office Action (see pages 6-8). Additionally, the newly submitted publication of Bermudes et al. in Exhibit A describes the use of several attenuated bacteria as delivery vectors, not any attenuated prokaryotic vector (not necessarily limited to attenuated bacteria).

B. With respect to rejections under 35 U.S.C. 103, once again Applicants presented essentially the same arguments as those already presented previously (e.g., examiner has not established a prima facie case of obviousness because he has not pointed to anything, in the cited reference or in the body of knowledge generally possessed by those skilled in the art, that would suggest the modification or combination of the references necessary to arrive at the presently claimed invention, particularly a method of enhancing the cytotoxic sensitivity of neoplastic cells to an antifolate drug). Additionally, Applicants argue that the Moscow patent teaches away from using other genes (such as FPGS) that may be involved in the acquisition of MTX resistance because Moscow et al. state that "decreased MTX uptake is the principal characteristic in many MTX-resistant cell-lines"; and that Applicants clearly distinguish the present invention from the teachings of Roy and Kim by the statement "It was unclear, however, whether increasing the FPGS expression of a tumor cell line already displaying intermediate FPGS enzyme activity would enhance the cell line's MTX susceptibility".

(1) The simple statement that "decreased MTX uptake is the principal characteristic in many MTX-resistant cell lines" is not deemed as an indication that Moscow teaches away from using other genes (such as FPGS) for reversing MTX resistance acquired by tumor cells, especially Moscow et al. clearly acknowledge that resistance to MTX in in vitro models can result from decreased folylpolyglutamate synthase (col. 1, lines 17-23), the transfection of a murine RFC gene partially reversed MTX resistance in the MTXZR 75-1 cells (col. 1, lines 52-54), and that the methotrexate resistance may be due to underexpression of reduced folate carrier protein (see abstract).

(2) It is also noted that none of the pending claims recites that a tumor cell displays intermediate FPGS enzyme activity.

(3) With respect to arguments previously presented, they are not found persuasive for the same reasons already discussed in the Final Office Action (see pages 13-16 and page 18).